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TEMPERAMENT DETERMINATION FOR MELATONIN: A BRIDGE FROM IRANIAN
TRADITIONAL TO MODERN SLEEP MEDICINE

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Abstract

History acknowledged Ibn Sina, or Avicenna, the author of the highly skilled textbook of medicine "Al-Qanun Fi Al-Tibb" or "The Canon of Medicine", as one of the greatest physicians in medicine. According to this medical textbook, the explanation of the existence of a cold temperament for sleep was that during sleep hours, people tended to have a movement of the nature of the body toward the inside, which caused the body to become cold during sleep. Temperament determination for molecules, including drugs, has proved several applications. The present study tried to demonstrate that the multitasking melatonin molecule, as a sleep related hormone, had a cold temperament. The consideration of this temperament for melatonin had the potential to connect and integrate Iranian traditional medicine to current medicine, and also opened new frontiers for the physiopathology of modern sleep medicine, based on traditional medicine.

Key words: Sleep ; Melatonin ; Iranian traditional medicine; Avicenna.

Heretofore, appreciable assays and efforts have been made by the publishers and authors of this journal to demonstrate the effect of different alternative medicinal plants on sleep improvement (Akanmu et al., 2005; Bum et al., 2004; Bum et al., 2011; Moto et al., 2011). In addition, there are numerous studies that provide evidence about the roles and functions of melatonin. This study describes melatonin temperament from the perspective of the Persian medicine pioneer Ibn Sina, also known in the Europe as Avicenna (980-1037 AD). Ibn Sina was an eminent Iranian physician and polymath who authored about 276 books on medicine, theology, physics, psychology, logic, music and mathematics. The most impressive of his works is "The Canon of Medicine (Al-Qanun fi al-Tibb or the Law of Medicine)" ,the most comprehensive five-volume medical encyclopedia of his time, which was originally written in Arabic language although Avicenna's mother tongue was Persian , " Al-Qanun fi al-Tibb " is similar to the modern medical texts regarding diseases classification, etiology, epidemiology, symptomatology and therapeutics (Choopani et al., 2012; Emtiazy et al., 2012b; Mosaddegh et al., 2012) .

Canon of Medicine remained a medical authority until the late 18th – early 19th century, and has been translated to many languages including Persian, Latin, Chinese, Hebrew, German, French and English. It had been used and taught in prestigious medical schools such as the University of Montpellier, France, until 1650. During the medieval era, many universities used it as a standard medical textbook .The principles of medicine described by the Canon 10 centuries ago are still taught at the University of California, Los Angeles and Yale University in the United States, among others, as part of the history of medicine. The influential Canadian physician, Sir William Osler, described the Canon as "the most famous medical textbook ever written "noting that it remained "a medical bible for a longer time than any other work" (Tajbakhsh, 2006).

One chapter of this textbook is dedicated to the study of sleep and wakefulness, as a topic regarding the human health.

Descriptions of the pineal gland date back to ancient times. Melatonin (N-acetyl-5-methoxy-tryptamine), a hormone produced in the pineal gland in the brain, regulates a number of physiological processes either by its powerful ability to scavenge reactive oxygen species, interact with intracellular molecules or via activation of the G protein-coupled melatonin receptors, MT1 and MT2. Melatonin regulates the immune system by influencing cytokine secretion, enhancing the production of several T helper cytokines and modulating the IL-2/IL-2R system. Platelet function is also regulated by the binding of melatonin to high-affinity sites, which results in enhanced platelet reactivity to physiological agonists and induces beneficial effects on platelet function and homeostasis. It also plays an important role in sexual maturation and neuroprotection, with anti-aging and anticancer effects as well. It has been shown that the

secretion of melatonin, as a prominent sleep-promoting agent, occurs mainly during nighttime, with rhythmic circadian pattern oscillations (Macchi and Bruce, 2004; Regodón et al., 2012).

The Iranian traditional medicine (Persian medicine) represents one of the oldest and prolific schools of traditional medicine. In order to have a broad perspective on the work of Avicenna, scholar of the Iranian traditional medicine, on sleep physiology, it is mandatory to discuss the fundamentals and principles of Iranian traditional medicine and to compare them to modern medicine.

In the concept of Persian medicine, everything or object in the universe is composed of four elements (*Air, Water, Fire and Earth*). Each of these elements is related to two qualities including hotness and wetness, coldness and wetness, hotness and dryness, and coldness and dryness respectively. On the other hand, the philosophy of Iranian traditional medicine is based on several principles, by which a person can be in an optimal health state, with minimum illness. One of these principles is "*Umure Tabiya*" (Natural Affairs), composed of seven parts, of which the second constituent is *Mizaj* (Temperament). Temperament is a mean quality, representing the consequence of the interaction of the four opposite primary qualities (*Wetness, Coldness, Hotness and Dryness*), residing within the abovementioned four elements. When the elements interact with one another through their qualities, they cause the emergence of a uniform and mean quality, designated as the temperament, which is present in equal proportions in every particle and component of the object. Therefore, every object all over the universe may have any of the above-mentioned qualities based upon its own specific temperament.

Traditional Persian medicine confers important applications to temperament. Drugs and foods are classified upon their temperaments. The temperament of a human being depends on the wet and fluid part of the body, which is derived from the digested food that is called *Akhlat* (humors), consisting of four types: *Dam* (blood), with hotness and wetness qualities, *Safra* (yellow bile), with hotness and dryness qualities, *Balgham* (phlegm), with coldness and wetness qualities, and *Sauda* (black bile), with coldness and dryness qualities. Each of these humors has similar characteristics to one of the four elements: *Dam* to *Air*, *Safra* to *Fire*, *Balgham* to *Water*, and *Sauda* to *Earth*. As a consequence, a person with a hot temperament is either *Damavi* (Sanguineous/Blood dominancy) or *Safravi* (Choleric/Yellow bile dominancy), while a person with a cold temperament may be *Balghami* (Phlegmatic/phlegm dominancy) or *Saudavi* (Melancholic/Black bile dominancy). Every human being has its specific temperament in concordance with the constituent humors he or she has. The body remains healthy when the humors have normal qualities and quantities. Any diversion from the described normal temperament can lead to a disease, a process better described in Iranian traditional medicine as *Sui e Mizaj* (dystemperament).

Another principle of Iranian traditional medicine is the *Tabiat* (Nature of the body) which is an innate capacity of the body that controls its equilibrium and homeostasis. Sleep is the tendency of *Tabiat* (which may be regarded here as the circulation of blood) toward the inside of body. The consequence of this directional flow is cooling of our body, especially at its surface, to the extent that one needs a blanket or coverlet during sleep (Shamsedin, 2005; Nazem, 2006; Emtiazy et al., 2012a). Therefore, the sleep temperament is assumed cold, because it produces a cold quality in our body.

In order to prove that melatonin, as a main sleep modulating molecule, has a cold temperament similar to the coldness of the sleep temperament, this study proposed several modalities.

Based on modern sleep medicine, the relationship between body temperature and sleep-wakefulness circadian rhythms is that people wake in the morning, when their body temperature begins to rise from its lowest level, and sleep during the night, when their body temperature begins to decrease in an opposite manner (Kohyama, 2011). Melatonin has a mild body temperature decreasing effect (Macchi and Bruce, 2004). Therefore, in consonance with Iranian traditional medicine, the melatonin temperament may be presumed cold.

It is worth mentioning that Avicenna has pointed out that, in order to attain a profound sleeping state, the bedroom must be dark and silent during sleep time (Shamsedin, 2005; Nazem, 2006), because the temperament of light is assumed hot in Iranian traditional medicine, and it disturbs and interferes with sleep, which is considered cold. On the other hand, modern sleep medicine has demonstrated that nocturnal bright light can suppress melatonin secretion (Macchi and Bruce, 2004; Gooley, 2011; Kohyama, 2011). Therefore, the temperament of melatonin is opposite to the temperament of light, which is hot. This effect becomes another argument to support the cold temperament for melatonin.

It has been documented that people with a hot temperament have a more intense sympathetic nervous system activity than those with a cold one (Shahbi et al., 2008). Among the disturbances of the autonomic nervous system, sympathetic hyperactivity, along with the hyperarousal associated with primary insomnia, have been reported in a recent study (Kohyama, 2011). Interestingly, the Persian school of traditional medicine claims that hot temperament people are more active and sleep less than cold temperament persons (Shamsedin, 2005).

On the basis of the above mentioned facts, it could be declared that that people with less amounts of endogenous melatonin are more prone to insomnia, meaning that these people may have a hot temperament. On the other hand, cold temperament people possibly have more levels of melatonin in their body, justifying the consideration that melatonin temperament is cold. Therefore, the latter individuals presumably sleep more, in comparison to hot temperament individuals.

It has been documented that pomegranate, strawberry and particularly cherry (*Prunus cerasus*) contain phytochemicals such as melatonin, which improve sleep duration and quality in healthy individuals (Badria, 2002; Howatson, 2011). Based on Persian traditional medicine (Ardekani, 2011), these fruits can produce a cold quality after

being consumed, and this may be mutually related to the hypothermic and soporific effect of melatonin on the human body, as described by modern medicine.

Finally, according to Iranian traditional medicine and considering Avicenna's viewpoint on the cold temperament of sleep, while connecting and integrating this concept to melatonin, one can suggest that the temperament of melatonin is also cold. The concept of temperament can be extrapolated to every molecule of the human body, representing an opening step toward the understanding of the past for today's application. Future articles will investigate other interesting perspectives of Persian sleep medicine in relation to modern physiology and also describe how Avicenna's concept may help to clarify the unknown etiologies of sleep related disorders such as insomnia, in particular.

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